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Neuroanatomical Correlates of Childhood Sexual Abuse: Identifying Biological Substrates for Environmental Effects on Clinical Phenotypes

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Sexual abuse during childhood is surprisingly common, with estimates in the general population ranging from 15% to 38% (1). It is associated with significant psychiatric sequelae, including the development of major depression and posttraumatic stress disorder (PTSD). These common consequences of exposure to trauma can emerge in the aftermath of natural disasters as well as those in which humans have a hand (2). Some responses, such as suicidal behavior, are not only life-threatening but have multigenerational repercussions, as individuals who report childhood sexual abuse are at risk not only for suicidal behavior themselves but also for transmitting suicidal behavior and mood disorders to their offspring (3). The timing (4) and severity of childhood sexual abuse are also relevant to its consequences (5). Earlier age at onset of childhood sexual abuse is associated with more intent during suicide attempts (6) as well as greater severity of PTSD (7) and depressive symptoms (8). Similarly, the severity of sexual abuse during development is reportedly related to earlier-onset suicidal behavior (6), greater depression severity (9), and more pronounced symptoms among patients with borderline personality disorder (5). Interestingly, other forms of early life stress, such as childhood emotional abuse and neglect, have been found to be stronger predictors of subsequent depression in adulthood than childhood sexual or physical abuse (10).

Following the excitement generated by the gene-environment interaction literature, researchers are now exploring the biological substrates that may mediate effects of early traumatic experiences on later psychopathology. Elegant studies in animal models have identified epigenetic mechanisms through which the early environment may induce enduring effects on gene expression and, with it, behavioral phenotypes (11). Reports of environmental effects on biological alterations more proximal to clinical phenotypes are also emerging, including effects on neurocognitive, neuroendocrine, and neuroimmune function.

Structural and functional neuroimaging provide powerful tools to explore long-term effects of life experience on neurodevelopment. Most, but not all, structural MRI studies examining neuroanatomical correlates of childhood sexual abuse thus far describe volume reductions in a variety of structures. Decreased volume of the corpus callosum, the left hippocampus, the anterior cingulate, the caudate nucleus, the amygdala, and the visual cortex, as well as more general decreased cerebral volume, have all been reported in survivors of childhood sexual abuse (for reviews, see references 12 and 13).

In this issue of the *Journal*, Heim et al. (14) make use of the burgeoning structural MRI technique of measuring cortical brain thickness to understand neuroplastic responses to childhood trauma. The authors studied 51 medically healthy women, of whom 55% (N=28) reported moderate-to-severe maltreatment, 18% (N=9) had PTSD, and 24% (N=12) had major depression. Cortical thinning was found to be present in the brain areas involved in the perception or processing of behaviors that are specific to the type of abuse experienced. For example, childhood sexual abuse was associated with cortical thinning in the genital representation field of the primary somatosensory cortex, whereas emotional abuse was associated with cortical thinning in regions linked to self-awareness and self-evaluation (15). The authors conclude that cortical adaptation to traumatic events may lead to decreases in the density of dendritic spines, leading to cortical thinning. They suggest that such changes relate to the child's sensory processing of the abusive experience, which alters cortical representation fields in a regionally specific fashion, based on the nature of the abuse itself. This finding comports with another recent work in which young adults, compared with an unexposed group, who witnessed domestic violence as children had decreased visual cortex gray matter (15), in terms of both volume and cortical thickness, regardless of whether or not they developed psychopathology. In addition, Heim et al. noted that age at onset, although not severity of childhood sexual abuse, was related to cortical thinning in the left temporal pole, the left parietal lobe, the left frontal pole, and the right frontal pole, areas associated with autobiographical memory among other functions. This, they postulate, may serve as the neuroanatomical basis for the observation that victims of childhood sexual abuse often have poor, if any, recollection of the experience and report overgeneralized memories. A question that arises from this finding is whether individuals who experience trauma at a later age, outside the window of peak vulnerability for cortical thinning, develop psychopathology through a mechanism that is distinct from the one responsible for consequences in those who experience trauma during an earlier, critical period.

What is the relevance of these neuroanatomical findings to the broader picture? If replicated, these data provide compelling evidence about the enduring structural effects on the brain as a function of early life experience that are not defined on the basis of a specific psychiatric diagnostic context. Given the nature of the environmental stressor and the difficulties in identifying victims at the time sexual abuse is occurring, it is unlikely that we will be able to develop longitudinal studies to more completely test the hypothesis. Nonetheless, this research may pave the way for the characterization of endophenotypes associated with trauma-related effects on the brain. The possible mechanisms the authors invoke to explain the neuroplasticity observed in this study may not be dependent on epigenetic effects and may suggest alternative molecular pathways underlying early life experience effects on neurodevelopment and psychopathology. Moreover, if life experience can have a role in brain restructuring during development, then appropriately timed experiential or behavioral interventions may have utility in mitigating the effects of negative environmental input or genetic deficits. Indeed, at the behavioral level, perceived social support protects against the development of adult depression among victims of childhood abuse (10). Consistent with this finding, murine studies suggest that enriched environments can mitigate the deleterious effects of low maternal licking and grooming behavior early in development (16). Of note, the question of whether the "active ingredient" of such enrichment is simply aerobic exercise (17), which is linked to hippocampal neurogenesis, has been recently raised.

Finally, if sensory input in general has the potential to precipitate neuroarchitectural restructuring, then observed dose effects of the environmental insults may be related to multimodal sensory input from the traumatic experience. Although it stands to reason that more severe experiences would have more profound effects on an individual, elucidation of the exact mechanism for this observation may uncover the neurophysiological basis of such a relationship.

Studies such as the one by Heim et al. bring us closer to delineating the mechanisms that lead to changes in brain morphology and function, which are so critical to developing effective behavioral and pharmacological interventions. We need to understand the role of several key elements leading to these neurobiological changes—the relative contributions of the severity, timing, and nature of a stressor in the context of genetic endowment. Equally important for future research is to study the role of resilience and its neurobiological underpinning, a sorely neglected area. The more clearly we can delineate a biological pathway from environment to psychopathology, the more likely we are to develop interventions to mitigate, cure, or even prevent what ails our patients.

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